**IN THE CLAIMS**

Please cancel Claim 9 and Claim 11.

Please amend the following claims.

C1

1. (Amended) A composition comprising an enzyme, wherein said enzyme comprises a heterologous functional domain, wherein said heterologous functional domain comprises an amino acid sequence that provides improved background specificity in a nucleic acid cleavage assay compared to said enzyme without said heterologous functional domain.

C2

52. (Amended) The kit of Claim 51, further comprising at least one RNA capable of hybridizing to said nucleic acid cleavage substrate.

## REMARKS

Claims 1-57 were originally filed in the present case. Claims 16, 17, 20-23, 45, 46, and 47 were cancelled by an Amendment filed December 13, 2001 ("Previous Amendment"). In response to the Examiner's restriction requirement, Applicants elected the group comprising Claim 1. In the Office Action mailed March 18, 2002, the Examiner indicated that the group comprising Claim 1 is termed Group I, Claims 1-15, 18, 19 and 50-57. Claims 24-44, 48 and 49 were withdrawn by the Examiner from further consideration pursuant to 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

The Examiner has asserted that Applicant elected the claims of Group I without traverse. However, Applicants noted in the Previous Amendment that the restriction was rendered moot by the cancellation, without prejudice, of Claims 16, 17, 20-23, 45, 46, and 47. Applicants further noted that these dependent claims cover subject matter encompassed by the independent claims that were not cancelled, and expressly indicated the intention to add claims back into the present case or a related case that explicitly recite one or more elements of the canceled dependent claims. As such, Applicants maintain that the election of the group containing Claim 1 was made with traverse.

Applicants have cancelled Claim 9 and Claim 11 for business reasons, and in order to further the prosecution of the present Application, yet without acquiescing to any of the Examiner's arguments, and while explicitly reserving the right to prosecute the original claims (or similar claims) in the future. A copy of the claims, as amended, is attached hereto at Appendix II for the Examiner's convenience.

In the Office Action dated March 18, 2002, the Examiner made several rejections. For clarity, the rejections at issue are set forth by number in the order they are herein addressed:

(1) Claims 1-15, 18, 19 and 50-57 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification is such a way as to enable one skilled in the art to make and/or use the invention;

(2) Claim 52 stands rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention;

(3) Claims 1-12 and 55-57 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by either of Brow et al., or Dahlberg, et al.; and

(4) Claims 1-15, 18, 19 and 50-57 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over either of Brow et al., or Dahlberg, et al.

Applicants believe the following remarks traverse the Examiner's rejections of the claims. These remarks are presented in the same order as the above rejections.

## I. Claims 1-15, 18, 19, and 50-57 Are Fully Enabled

Claims 1-15, 18, 19 and 50-57 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification is such a way as to enable one skilled in the art to make and/or use the invention (Office Action, pgs 2-3). In particular, the Examiner indicated that the specification does not provide an explanation for notations in Tables 2-7 ("IdT, %Tth", "%Taq4M", "HP", and "X"), or an indication of the significance of "cycling rate" or "turnover rate" in these figures (Office Action, pg 3).

Applicants respectfully disagree with this rejection, and submit that even if these figure legends were not clear (which they are as explained below) this is not relevant to

enablement of the claimed compositions. The claims are directed toward kits and compositions comprising particular enzymes. The specification provides more than adequate guidance on how to make and use these kits and compositions (See, e.g. the Examples in the Specification). The tables the Examiner refers to simply add additional support for the claims. Nonetheless, Applicants have addressed the Examiner's table legend rejection below making it clear that explanations for each these terms are found within the Specification.

For example, the terms "IdT", "HP" and "X" refer to test substrates having particular structures. These test substrates are shown in the drawings and are described in Example 1 (starting on page 50 at line 25), which provides a method of rapidly screening cleavage activity of nucleases on a number of cleavage structures. The IdT and IrT1 structures are described on page 55 of the specification. Specifically, line 13 indicates that these structures are shown in Figure 24, and line 17 provides the particular sequence identifiers for each molecule. Similarly, the HP structure is described on page 56 at lines 3 and 7, and the X structure is described on page 54 at lines 22 and 26-27. The HP structure is shown in Figure 22A (as indicated on p 56, line 6) and the X structure shown in Figure 22B (as indicated on p56, line 7). As such, the specification clearly describes the structures being referred to in Tables 2-7.

The terms "turnover rate" and "cycling rate" are used interchangeably throughout the specification. As noted in several examples, such as in Example 1 at page 56, lines 21-22, the turnover rate is defined as the number of cleaved signal probes per target molecule, per minute in the conditions tested. For convenience, a comparison of the turnover rates between the test nuclease and one or more reference nucleases are provided in these tables, with the activity of the test enzyme indicated as a percentage of the reference activity. The comparison of the enzymes being screened or tested to reference or control enzymes is discussed in Example 1, at page 52 at lines 3-7. One skilled in the art, reading the Specification, would understand "%Tth" and "%Taq4M" as referring to the activity of the test enzyme indicated as a percentage of the activity of Tth enzyme or the Taq4M enzyme, respectively, tested under the same conditions.

As detailed above, the subject matter of Claims 1-15, 18, 19 and 50-57 is described in the specification is such a way as to enable one skilled in the art to make and/or use the invention. As such, Applicants respectfully request that this rejection be withdrawn.

## II. Claim 52 is Definite

Claim 52 stands rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention (Office Action, page 3). Applicants note that Claim 52 has been amended in order to correct the typographical error "at" in the claim. The amendment is made to correct this typographical error and to further Applicants' business interests and the prosecution of the present case, yet without acquiescing to the Examiner's rejection. Claim 52 as amended is definite. As such, Applicants respectfully request that this rejection be withdrawn.

## III. Claims 1-12 and 55-57 are Not Anticipated

Claims 1-12 and 55-57 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by either of Brow et al., or Dahlberg, et al. (Office Action, page 4). Applicants respectfully disagree. The Examiner has asserted that the alterations to the polymerases disclosed by Brow and Dahlberg fall within the definition of "heterologous functional domain" defined in the present Application, and that polymerases having reduced synthetic activity have the "improved nuclease activity" claimed in the present Application (Office Action, page 4). Applicants respectfully disagree.

However, for business reasons and in order to further prosection of the present application, but without acquiescing to the Examiner's arguments, and reserving the right to prosecute the same or similar claims in the future, Applicants have amended Claim 1 to recite an enzyme comprising a heterologous functional domain wherein said heterologous functional domain "comprises an amino acid sequence that provides improved background specificity in a nucleic acid cleavage assay compared to said enzyme without said heterologous functional domain."

For the Examiner's convenience, Applicants note that support for "improved background specificity" is found throughout the specification, e.g., on page 20, lines 4-5. Examples of some ways of testing background specificity of the claimed enzymes in provided in Experimental Example 1, e.g., on page 54 starting at line 22 ("Rapid screen: background specificity X structure substrate"), and on page 55, starting at line 3 ("Rapid screen: background specificity hairpin substrate").

Neither Brow nor Dahlberg disclose or contemplate enzymes comprising heterologous functional domains comprising an amino acid sequence that provides improved background specificity in a nucleic acid cleavage assay, or kits comprising such enzymes. Therefore, neither reference discloses every element of independent Claims 1 or 50, nor every element of any claim depending therefrom. As such, Applicants respectfully request that these rejections be withdrawn.

## IV. Claims 1-15, 18, 19, and 50-57 are Not Obvious

Claims 1-15, 18, 19 and 50-57 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over either of Brow et al., or Dahlberg, et al. for the same reasons cited in the 102(b) rejection discussed above (Office Action, page 4). The Examiner asserts that the additional limitations of providing the heterologous functional domains in the palm or thumb region, would have been obvious. Applicants disagree with this rejection and submit that this rejection is moot in light of the amendment to Claim 1.

As noted above, Claim 1 has been amended to recite an enzyme comprising a heterologous functional domain wherein said heterologous functional domain comprises an amino acid sequence that provides improved background specificity in a nucleic acid cleavage assay. Neither Brow nor Dahlberg teach or contemplate enzymes comprising heterologous functional domains comprising an amino acid sequence that provides improved background specificity in a nucleic acid cleavage assay, or kits comprising such enzymes. As such, no *prima facie* case of obviousness could be established because, for example, the art cited by the Examiner does not teach or suggest all of the claim limitations of Claims 1-15, 18, 19, and 50-57 (See, MPEP 2143). As such, Applicants respectfully request that this rejection be withdrawn.

## CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: July 18, 2002

Jason R. Bond
Registration No. 45,439
MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, California 94105

## APPENDIX I

## VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A composition comprising an enzyme, wherein said enzyme comprises a heterologous functional domain, wherein said heterologous functional domain comprises an amino acid sequence that provides improved background specificity compared to said enzyme without said heterologous functional domain [provides altered functionality] in a nucleic acid cleavage assay.

52. (Amended) The kit of Claim 51, further comprising at least one RNA capable of hybridizing to said [at] nucleic acid cleavage substrate.

## APPENDIX II

## COMPLETE SET OF PENDING CLAIMS

1. A composition comprising an enzyme, wherein said enzyme comprises a heterologous functional domain, wherein said heterologous functional domain comprises an amino acid sequence that provides improved background specificity in a nucleic acid cleavage assay compared to said enzyme without said heterologous functional domain.

2. The composition of Claim 1, wherein said enzyme comprises a 5' nuclease.

3. The composition of Claim 2, wherein said 5' nuclease comprises a thermostable 5' nuclease.

4. The composition of Claim 1, wherein said enzyme comprises a polymerase.

5. The composition of Claim 4, wherein said polymerase is altered in sequence relative to a naturally occurring sequence of a polymerase such that it exhibits reduced DNA synthetic activity from that of the naturally occurring polymerase.

6. The composition of Claim 4, wherein said polymerase comprises a thermostable polymerase.

7. The composition of Claim 6, wherein said thermostable polymerase comprises a polymerase from a *Thermus* species.

8. The composition of Claim 7, wherein said *Thermus* species is selected from *Thermus aquaticus*, *Thermus flavus*, *Thermus thermophilus*, *Thermus filiformus*, and *Thermus scotoductus*.

10. The composition of Claim 1, wherein said heterologous functional domain comprises an amino acid sequence that provides an improved substrate binding activity in said nucleic acid cleavage assay.

12. The composition of Claim 1, wherein said heterologous functional domain comprises two or more amino acids from a polymerase domain of a polymerase.

13. The composition of Claim 12, wherein at least one of said two or more amino acids is from a palm region of said polymerase domain.

14. The composition of Claim 12, wherein at least one of said two or more amino acids is from a thumb region of said polymerase domain.

15. The composition of Claim 12, wherein said polymerase comprises *Thermus thermophilus* polymerase.

18. The composition of Claim 1, wherein said nucleic acid cleavage assay comprises cleavage of a DNA member of a substrate containing at least one RNA component.

19. The composition of Claim 1, wherein said nucleic acid cleavage assay comprises an invasive cleavage assay.

50. A kit comprising the composition of Claim 1.

51. The kit of Claim 50, further comprising at least one nucleic acid cleavage substrate.

52. The kit of Claim 51, further comprising at least one RNA capable of hybridizing to said nucleic acid cleavage substrate.

53. The kit of Claim 50, further comprising a labeled oligonucleotide.

54. The kit of Claim 50, further comprising an invasive oligonucleotide.

55. A method for cleaving a nucleic acid comprising:

a) providing:

i) the enzyme of Claim 1; and

ii) a substrate nucleic acid; and

b) exposing said substrate nucleic acid to said enzyme.

56. The method of Claim 55, wherein said exposing said substrate nucleic acid to said enzyme produces at least one cleavage product.

57. The method of Claim 56, further comprising the step of c) detecting said cleavage product.